A Lecture

ON

"HOW DO DRUGS ACT?"*

BY

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Towards the end of last century there was a school of medical thought growing up with a profound scepticism as to the value of drugs. The reaction against this began when Starling enunciated his theory of hormones. Whenever we give a drug we imply thereby a belief that the functions of the body can be influenced by chemical means, and we found fresh support for that confidence in the fact that the body was now shown to produce chemical substances whereby it regulated its own functions. Since then another important group of intensely active chemical substances essential to our well-being has been discovered in the vitamins. The animal body has, however, very little power of manufacturing these—we are dependent on vegetable life in the main for them; they are mostly exogenous hormones.

CHEMICAL SUBSTANCES AND NERVOUS ACTIVITY

In those instances where hormones have been isolated they prove to be of comparatively simple chemical structure. We know that adrenaline is manufactured by the medullary cells of the adrenals, which are actually formed out of sympathetic ganglion cells. Langley showed that the effect of adrenaline on any part is the same as if the sympathetic nerves to that part were stimulated—an extraordinarily interesting example of a chemical substance imitating a nervous one. Now although adrenaline has no effect on a structure which has never received a sympathetic innervation, Elliott found that cutting off that innervation does not abolish the effect of adrenaline on a structure which has once possessed it. On the contrary, its effect is actually increased. For this reason both Langley and Elliott independently put forward the theory of a receptive substance beyond the nerve ending, on which the drug acted.

In 1907 W. E. Dixon showed that after stimulating the vagus nerve to the heart a substance could be extracted from the heart muscle which was inhibitory in its action on other heart muscle, and could be antagonized by atropine, just as atropine antagonizes vagus stimulation. This accords with the well-known effect of atropine in checking other secretions. Unfortunately, this work of Dixon's met with so much scepticism that he dropped the subject. This work was subsequently revived and extended by Dale, and in 1921 by Loewi. It was proved that the substance produced was acetylcholine, and that it was liberated not only when the vagus to the heart was stimulated, but whenever any parasympathetic fibres came into action.

Now it is known that physostigmine—or eserine, as it is often called in clinical work—imitates the effect of parasympathetic stimulation. Thus either stimulating the third cranial nerve or instilling eserine will contract the pupil. Loewi has shown that this is because eserine prevents the blood or the tissue cell from destroying the acetylcholine produced. Apparently, then, atropine and eserine act by interfering with and expediting respectively the normal chemical results of parasympathetic stimulation. It is important to note that if atropine be given and the vagus subsequently stimulated, just as much acetylcholine is produced as before, but the atropine prevents it from getting into the receptive substance.

In the same way sympathetic stimulation has been found to produce an adrenaline-like substance in other structures besides the adrenal medulla. I say adrenaline-like, for Cannon has shown that it is not exactly the same as adrenaline. Some sympathetic effects are stimulating, others inhibitory. While adrenaline reproduces all these, Cannon has extracted a slightly different chemical substance as the result of an excitant action from the one appearing after an inhibitory action. He calls these "sympathin E" and "sympathin I" respectively, and looks forward to making two similar brands of adrenaline. The "E" form could be used to stimulate the heart and to raise blood pressure without inhibiting digestion. The "I" variety could be used for relaxing bronchial spasm without raising the arterial pressure or the concentration of sugar in the blood. This would be a further step in the direction of natural therapeutics.

It appears, then, to be a general rule that nervous stimuli may liberate chemical substances which transform a nervous stimulus into a chemical reaction, or, in Hopkins's illuminating phrase, that "substances produced temporarily and locally, by virtue of their chemical properties, translate for the tissues the messages of nerves."

Now just as the appropriate chemical material may get into this receptive substance so may a toxin. G. N. Myers at Cambridge has recently shown that a therapeutic drug may seize on the receptive substance, and thus bar the way to the ingress of the toxin. He found, for instance, that the diphtheria toxin could be prevented from attacking the heart if digitalis were given first. This resolves a clinical and pharmacological conflict. The pharmacologist has maintained that digitalis cannot exert its usual effect on the toxic heart, but the clinician still continues to administer it, and claims good results. Now we see that though digitalis would have to be given prophylactically to produce its full effect, if it is got in early it can still bar the way to the toxin swamping the heart. It seems to me that the pharmacology of the future will have to concern itself with the natural history of these receptive substances, and find out in what way they can be helped by drugs both positively, by facilitating their reactions, and negatively, by blocking the way against the entrance of toxins.

THE ENDOCRINES

The pituitary provides some interesting sidelights on this relationship between nervous and chemical stimuli. When in 1913 it was found that injections of pituitrin would relieve the symptoms of diabetes insipidus it seemed natural to conclude that this disease was due to deficient action of the posterior lobe of the pituitary. Then cases were described in which there was no damage to the pituitary, but a lesion in the overlying diencephalon, and so a purely nervous theory of the aetiology of diabetes insipidus was put forward. But an injection of pituitrin will control the output of water even by a denervated kidney. Clearly, when the lesion is purely nervous it acts by upsetting the normal chemical response of the gland. Indeed, it is generally recognized to-day that diabetes insipidus may result alike from a lesion of the gland or the overlying nervous structures, or of the stalk which connects them. Pituitrin is also known to start the flow of milk from the mammary gland. Leslie Pugh found that if a cow, as not infrequently happens, refused to give her milk because she disliked the dairyman, an injection of pituitrin made it impossible for her to be thus recalcitrant. Her emotional reaction had checked her secretion of pituitrin, but the injection cut under this nervous inhibition, and perforce the milk flowed in answer to a purely chemical reaction.

* Delivered before the City Division of the British Medical Association.

Endocrines also illustrate the way in which drugs antagonize one another. Pituitrin is antagonistic to insulin, but this antagonism is not a directly chemical one. It is carried out through the intermediary of the liver. Pituitrin, or, more strictly, its vasopressin moiety, empties the glycogen reservoirs in the liver, while insulin stores dextrose there as glycogen. Adrenaline is antagonistic to insulin in precisely the same way, thus explaining emotional glycosuria. The antagonism of thyroxine to insulin is rather different: by quickening up the whole of metabolism, including that of the liver, the glycogen there is converted into sugar.

Endocrinology further exemplifies another way in which drugs may act—that is, by increasing or diminishing the action of a hormone. In Graves's disease we have every sign of an overacting sympathetic. Thyroxine lowers the threshold for sympathetic stimulation, thus exaggerating the response. Quinine hydrobromide tends to antagonize this effect, and incidentally the tolerance of the patient with Graves's disease is extraordinarily high for this drug. The more thyroxine secreted, the more difficult it is to produce cinchonism. Then consider iodine therapy. The first effect of iodine shortage is thyroid enlargement. Giving iodine helps the gland to return to a more resting state. It is curious that it should also help in hyperthyroidism, as it undoubtedly does. Harington's recent researches show that this is not, as was suspected, due to the thyroxine secreted in Graves's disease being unsaturated with iodine, and therefore more toxic until it was so saturated. But I will not go into that difficult subject further than to say that recent observations at the Middlesex Hospital seem to show that you can saturate the thyroid of exophthalmic goitre with iodine in a fortnight, and that it will remain saturated for six weeks.

From the obvious effects of iodine on the thyroid it has been claimed that the therapeutic effect of iodine or iodides is entirely due to their altering the state of activity of the thyroid gland. This is probably too narrow an interpretation: note the purely chemical influence of iodide in rendering a metallic compound more soluble, and thus eliminating it more readily from the system—for example, mercury and lead, or toxins such as that of syphilis. May it not act in the same way in removing less recognized toxic substances? Thus iodide does not lower normal blood pressure, but does lower raised blood pressure. Is it by elimination of pressor amines absorbed from the bowel?

The elimination of lead raises the question of the action of another hormone—parathormone. We know that this mobilizes calcium from the bone into the blood stream. In chronic plumbism lead is also stored in the bone, and parathormone can be used to eliminate it thence. Workers in radium have suffered grievous damage from its storage in their bones, with resulting aplastic anaemia, just as has occurred in *x*-ray workers. Here, too, parathormone may help in elimination of a heavy metal. In parenthesis I may remark as germane to my subject that our whole treatment of the anaemias has been revolutionized in the last few years by the discovery that certain substances are necessary for the different stages in the maturation of the red blood corpuscle. Liver extract acts on a different phase from the one that iron acts upon.

But to revert to parathormone and the calcium balance. If the blood calcium is too low we know that tetany and a general irritability of nervous tissues result. If it is too high, among other effects there is muscular weakness through inability of nervous stimuli to produce their normal response with their normal ease. This calcium balance is maintained by parathormone and vitamin D, which act, however, in very different ways. The first effect of an increased supply of parathormone is a lowering of blood phosphorus, followed by a withdrawal of calcium from the bones and an increased excretion of calcium, which is, however, insufficient to prevent the blood calcium from keeping at an abnormally high level. Vitamin D, on the other hand, directly increases the net calcium absorption from the alimentary tract.

Action of Vitamins

This question of calcium balance leads to a further consideration of vitamin D. The long controversy as to rickets, whether a disease of the dark or a dietetic disorder, was solved—as such controversies between sincere workers often are—by finding that both were right. We know now that if a diet contains too little vitamin D and an excess of cereals, rickets results, but that light of certain wave-lengths, such as is emitted by the mercury vapour lamp, will largely correct this. When the British mission was working in Vienna after the war it was observed that the child in the one bed in a ward on which direct sunlight fell without the intervention of glass improved more quickly than the others. Only a narrow part of the spectrum is effective, and glass will stop these waves. Then came the direct proof that sunlight or suitable irradiations will convert ergosterol into calciferol, which is apparently vitamin D itself. And thus was reached the rational explanation of the therapeutic value of cod-liver oil, so long demonstrated empirically. Just as haemoglobin carries the oxygen of the air into the deepest tissues of the body, so does vitamin D carry sunlight to its darkest parts. Even irradiating the sawdust in the cages of rats deprived of this vitamin is sufficient to protect them against rickets if they eat it, as they usually do.

Dr. Harriett Chick's opinion is that the only effective use of ultra-violet rays is when it is desired to raise the calcium content of the blood. We may conclude that the most important function of vitamin D is to regulate the calcium metabolism of the body, and that the recognition of this fact must underlie all attempts at calcium therapy.

Though hypervitaminosis is not possible with natural foods, such concentrated vitamin preparations as are now available may do harm in that direction. Thus 1 mg. of calciferol daily is ample for therapeutic purposes, while 4 mg. a day have produced renal calculi. In the light of our present knowledge it would appear that parathormone should be reserved for emergencies when it is necessary rapidly to raise the level of calcium in the blood. Yet parathyroid is still widely prescribed for conditions where vitamin D is a simpler and more effective remedy. Interesting work is, however, being done for such conditions as osteitis deformans by first mobilizing calcium salts from the bones by parathormone and then redepositing them by graduated doses of vitamin D.

But you will not wish me to detail the uses of vitamins. I should like to discuss, however, the light that recent work on vitamin A has thrown on certain therapeutic problems. I have already said that animals have but little power of manufacturing vitamins; they can, however, convert certain pro-vitamins into vitamins—for example, carotene into vitamin A and ergosterol into vitamin D. Carotene is the yellow pigment widely distributed in coloured vegetables, which is converted into vitamin A in the liver. Early in the history of vitamins it was recognized that this particular one was necessary to the proper nutrition of the cornea. The Mellanbys have shown that we can state more generally that vitamin A is necessary for the proper nutrition of epithelium in general.

Thus, although we know the importance of vitamin D in preventing dental caries, it is only recently that Mrs. Mellanby has shown that a shortage of vitamin A leads

to a keratinization and thickening of the periodontal membrane; the faulty development which follows is a factor in the pyorrhoea of later life. Thus a lack of vitamin A spells pyorrhoea, while a lack of vitamin D spells dental caries. Such changes in epithelial and glandular tissues diminish the resistance to microbic invasion everywhere. That is probably the basis for the claim that vitamin A is an anti-infective agent. It really does this simply by maintaining a natural barrier of a healthy epithelium. But Professor Mellanby has shown another very important thing about vitamin A. In its absence an animal will develop lesions of tracts in the spinal cord, similar to those seen clinically in subacute combined degeneration. Wheat germ or ergot will increase this, but it can be completely overcome by adequate doses of vitamin A.

Now we know that clinically subacute combined degeneration and pernicious anaemia often go together. In both we have achlorhydria and the absence of Castle's intrinsic factor in the gastric mucosa. Though liver extract improves the blood picture it does not improve the cord symptoms. Ungley and Susman maintain, however, that this is because the extract, as prepared, lacks vitamin A, and they claim that whole liver, which contains it, will ameliorate the changes in the central nervous system. Though this is not universally accepted, one can see that it is quite possibly the case. W. W. Sargent has described instances recently where liver extract alone improved the blood picture as usual, but the cord changes got worse; on iron alone the blood picture deteriorated, but the spinal cord improved. He has even reported similar nervous symptoms in chronic microcytic anaemia which have cleared up on massive doses of iron.

This is the interesting position which has arisen. The rigid dictum that a tract in the cord which has once degenerated can never recover no longer holds. Lack of vitamin A can produce them, abundance of vitamin A can cure them. How do they occur in a patient who is on an ordinarily mixed diet, and therefore receiving an amount of vitamin A which is ordinarily adequate? Does the absence of HCl and Castle's intrinsic factor prevent the body from utilizing vitamin A, just as it prevents the proper maturation of the red blood corpuscle? Do massive doses of iron in some way enable the body again to make use of the vitamin A presented to it? It is beginning to look like it. The actual daily needs of the body for iron are small, yet all recent observers are agreed that for the nervous symptoms and for the cure of microcytic anaemia 160 grains of Blaud's pill or 90 grains of ferri et ammon. cit. are required in the day, and that a comparatively small reduction in the dose does away with its effectiveness. The conclusion seems almost inevitable that these large doses of iron in some way simply facilitate the utilization of vitamin A which, from one cause or another, the body has lost. One might compare with this the rickets, the pellagra-like rash, and the large-celled anaemia, which may occur in coeliac disease. Here there is a failure to absorb fats, and hence a shortage of fat-soluble vitamins, so changes resembling those of a mixture of deficiency diseases occur, even on a normal diet. Why the intestinal mucosa fails to absorb fat is still unknown, but apparently it is still capable of absorbing the concentrated vitamins.

In his Linacre Lecture at Cambridge last May, Mellanby reported some further remarkable facts. He showed how lack of vitamin A led to changes in the posterior root fibres, though to hardly any in the anterior root. This special sensitivity on the part of sensory fibres to vitamin lack is also seen in the optic nerve, and is apparently responsible for night-blindness. The visual purple extracted from the retinae of animals suffering from lack of vitamin A fails to regenerate at the normal rate. Here is a wide field for research in the therapeutics of organic nervous disease, a subject which confessedly has so far been a gloomy one. We may conclude that the study of the way in which drugs may help or hinder vitamin actions is full of hope, just as is the study of their effect on hormones and the receptive substances between the nerve ending and the responsive tissue.

These therapeutic effects of vitamins and hormones illustrate another point—the potency of the minute dose. When someone asked me how I imagined that I could produce any influence on the body by giving five grains of a drug, I replied that the body itself worked with fractions of a milligram. The potency of a hormone is enormous. Abel's extract of the posterior lobe of the pituitary can produce contraction of the uterus when one part is dissolved in 15,000 million parts of water—one grain in 1,000 tons of fluid! This might be claimed as a point for homoeopathy. There is no doubt that Hahnemann had some valuable ideas, even if some of his premisses were faulty. The symptom as an expression of something which needed to be assisted rather than repressed; the value of expectant treatment; the efficacy of small doses—all these were progressive conceptions. The whole system of active immunization by vaccines is based upon aiding the symptomatic expression of the body's attempts to throw off the disease. But to my mind the homoeopathic ideal has been spoiled by being crystallized into a creed. That is fatal to progress, as is shown by the failure of homoeopathy to add anything to our knowledge in pathology or in diagnosis—subjects which it might be thought were common both to the orthodox and to the homoeopath. I know of only one apparatus they have added to our armament—Dudgeon's sphygmograph.

Chemical Structure and Physiological Action

Vaccines apparently cause a reaction in living tissues leading to the formation of a new effective substance. So do some drugs—for instance, emetine in dysentery and salvarsan in syphilis; both are ineffective against the appropriate parasite *in vitro*. Therefore the specific effect of a drug usually depends upon its chemical interaction with some constituent of the living cell. It was therefore hoped that it might be possible to correlate physiological action and chemical constitution, but to a large extent the attempt has yielded disappointing results. In one instance a definite relationship between physical state and physiological action has been made out. Certain hypnotics are relatively inert substances, and may differ widely chemically, but they have this in common, that they are soluble in fat and other lipoid compounds, and so tend to collect especially where such compounds exist—that is, the central nervous system, thus interfering with the normal working of the nerve cells. However, as Hopkins recently pointed out, the investigation has been one-sided, and should involve consideration of the structure of the cell as well as that of the drug. Quite recently a striking instance of association between physiological action and chemical structure has been demonstrated, largely through the work of Dodds. Oestrin, the ovarian hormone; calciferol, which has such an influence on the orderly growth of bone; and the carcinogenetic substances to be found in tar, all contain the condensed carbon rings which we call anthracene. Thus it appears that normal reproductive activity, normal growth of bone, and that irregular, disorderly, unrestrained growth which constitutes malignancy are alike conditioned by this condensed ring, chemical alterations in it, apparently merely of hydrogenation, leading to extraordinarily different types of growth. The whole subject assumes fresh interest when we recall that anthracene is normally a coal-tar derivative, and was therefore formed under the influence of sunlight

ages ago, just as calciferol has been formed in our own subcutaneous tissues by the bright sunlight of this summer.

Conclusion

I have tried to indicate some of the general principles underlying the action of drugs, the difficulties that are encountered in their study, and the problems that have still to be solved. I have not touched on such topics as idiosyncrasy and tolerance. It is still true that to a large extent we have to remain empirical in our use of drugs. In some instances empirical success has been followed long after by a rational explanation, such as the effect of mercury and arsenic in syphilis, ipecacuanha in amoebic dysentery, quinine in malaria, and cod-liver oil in rickets. In others the explanation is still to seek, such as salicylate in rheumatism and colchicum in gout. I am therefore constrained to utter a plea for empiricism, especially as I still remember the scorn of the pharmacologist for the clinical belief in cod-liver oil before vitamins were discovered. And in conclusion I will quote Timme's reminder that "the abysmally ignorant South American savages who gave us cinchona bark for malaria did not even know the formula for quinine."

THE HOUSING PROBLEM

WITH SPECIAL REFERENCE TO THE PRESENT POSITION *

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The housing problem, which includes the slum problem, is a highly complex one, and the Acts of Parliament and the Government circulars affecting it are so numerous and have been so often amended or repealed that it is difficult for anyone not specially versed in the subject to keep fully up to date. In this paper it is proposed to deal with the subject as simply as possible on the assumption that most medical practitioners, however interested they may be, have far too many other subjects occupying their minds to be able to devote much time to the intricacies of the housing question. Members of the medical profession—more perhaps than any others—must be fully alive to the evils associated with bad housing, and must necessarily desire to see drastic and far-reaching improvements effected. At the same time, the point of view of the medical profession will be rather different from that of many others who are interested in housing, for doctors see the human side of the problem at close quarters.

A vast amount of money has been spent since the war in the building of houses, yet the housing problem, in so far as the poor are concerned, is still unsolved. The slums and the slum dweller are still with us; a great shortage of houses at rents within the reach of the poor persists, and overcrowding of the worst sort is rife. This leads me to the first point I want to insist upon—namely, that the housing problem to-day is essentially the problem of housing the poor. The medical profession, I feel sure, will heartily endorse this, but until recently it has not generally been recognized or acted upon. I think we may say that it was largely the recognition of this aspect of the case which led the present Government to withdraw, rightly or wrongly, the subsidy under the Act of 1924 (the Wheatley Act) for the building of "ordinary" working-class houses, and, at the same time, to concentrate upon the building of houses for slum clearance.

* Read in opening a discussion in the Section of Public Health at the Annual Meeting of the British Medical Association, Dublin, July, 1933.

The 1933 Housing Act

The Housing (Financial Provisions) Act, 1933, which has just been passed, is probably, in relation to the importance of its provisions, the shortest Housing Act ever passed. It contains only three sections, one of which is purely formal, fixing the title of the Act. The first section repeals the Wheatley subsidy; the second gives substantial encouragement to building societies by authorizing local authorities and the Government to share with them the risk entailed in advancing a higher proportion of the building costs of new houses than they would otherwise have felt justified in doing. It is hoped that, in practice, this will mean that building societies will be willing to advance up to, say, 90 per cent. of the cost instead of only about 70 per cent. Schemes for building under this arrangement will have to be approved by the Minister of Health, and the houses so built must be "intended to be let to persons of the working classes." Moreover, the houses must conform to an approved standard as regards type and superficial area, and must not (except under very special circumstances) exceed twelve to the acre, while each house must be provided with a bath. The Act makes no new provisions with regard to slum clearance except in so far as the withdrawal of the subsidy on the building of ordinary working-class houses will undoubtedly encourage local authorities to concentrate all their efforts on building houses to replace those demolished in connexion with slum clearance. This, indeed, is the clearly avowed object and intention of the Government.

In Circular 1331, issued on April 6th last, the Minister states:

> "In the view of His Majesty's Government the present rate at which the slums are being dealt with is too slow, and they look for a concerted effort between the central Government and the local authorities immediately concerned to ensure a speedier end to the evil, and an end within a limited time. His Majesty's Government are further of opinion that present conditions are favourable to the success of a vigorous campaign of slum clearance."

Local authorities are therefore urged:

(*a*) To prepare and adopt a programme, the component part of which should be:

(1) A list of areas in which clearance is necessary, with information of the number of houses to be demolished in each, and of the number of the inhabitants;
(2) A list of the areas in which improvement by way of reconditioning or otherwise is necessary, with information as in (1) above;
(3) A time-table of the initiation, progress, and completion of action to secure clearance or improvement, as the case may be, of all these areas;
(4) A time-table of rehousing co-ordinated with the displacements contemplated by the time-table of clearance operations.

(*b*) To make an immediate beginning with the programme by the declaration as clearance or improvement areas of such areas as can be immediately dealt with, and by making the necessary orders."

The Minister asks to be supplied with a copy of the programme adopted not later than September 30th next, and he suggests that, as far as practicable, programmes should be so arranged as to be capable of achievement within five years. The circular adds that while slum clearance on a large scale may be necessary only in a limited number of large towns, there are few towns, or even villages, in which there is not urgent need for some action.

The Minister of Health (Sir Hilton Young) has supplemented his departmental documents by personal utterances both in and out of the House of Commons.